Friday Report: Issue 68

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COVID-19 Actuaries Response Group – Learn. Share. Educate. Influence.

COVID-19 is still one of the hottest topics for scientific papers and articles. The COVID-19 Actuaries Response Group produces an update on the last Friday of every month with a summary of key papers, articles and data.

Vaccines

FDA authorisation of vaccines for children (link)

On 17 June, the U.S. Food and Drug Administration authorised emergency use of the Moderna and the Pfizer-BioNTech COVID-19 Vaccines in children down to 6 months of age. Previously the authorisation had extended down to 18 years of age for Moderna and to 5 years of age for Pfizer-BioNTech.

The effectiveness and safety data evaluated and analysed by the FDA were generated in ongoing, randomised, blinded, placebo-controlled clinical trials. Effectiveness was assessed primarily via measuring immune response in the children and comparing these to immune response observed in young adults. Analysis of the occurrence of COVID-19 cases was determined not to be reliable due to the low number of COVID-19 cases that occurred in study participants.

Safety was assessed via follow-up of at least 2 months among both recipients of vaccine and placebo and longer-term safety follow-up is ongoing for the study participants.

Moderna reports on successful trials of Omicron specific vaccine (link)

Phase 2 and 3 trials of an Omicron specific booster vaccine mRNA-1273.214 by Moderna have met all primary endpoints (including safety) the company has announced, when its antibody response against Omicron was compared with a booster dose of its original Spikevax vaccine mRNA-1273. In addition, the vaccine gave an improved response against the ancestral strain and all prior common variants compared with its original vaccine.

Additionally, Moderna expects that the effectiveness will be more durable than using the original as a booster, and intends to provide a 3-month update in due course.

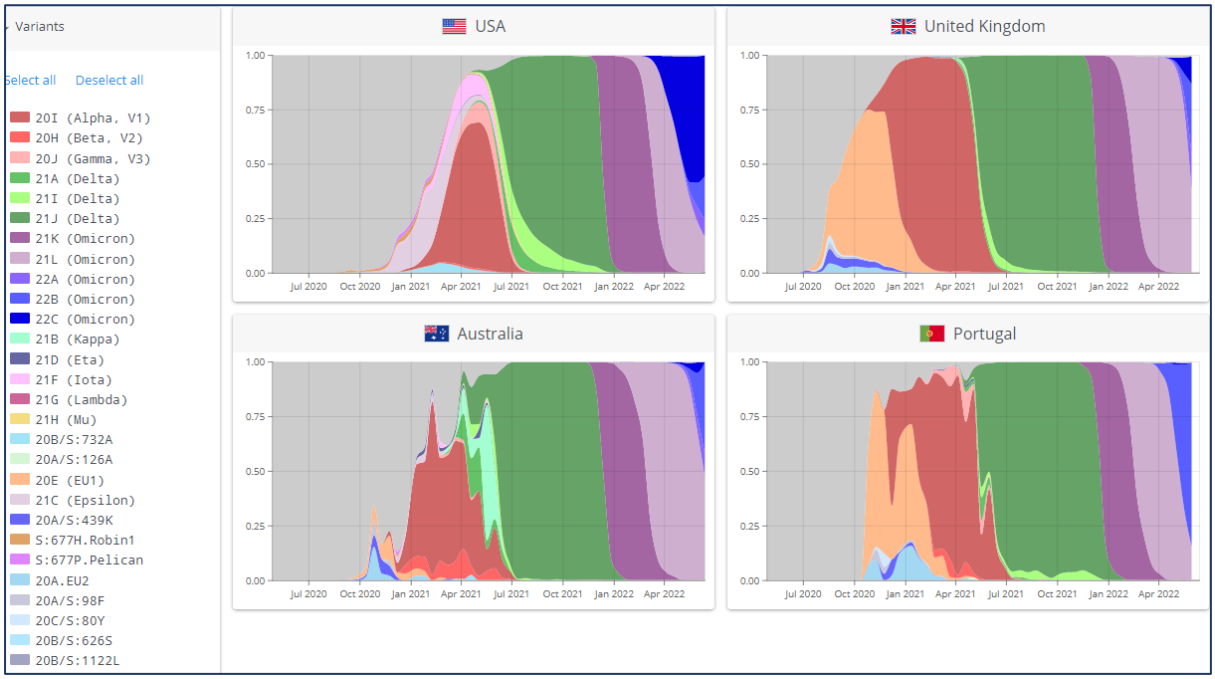
The company is hopeful that the vaccine will be a lead candidate for use as a booster this autumn.

Variants

Frequency of Sequences of Omicron Sub-lineages

In previous Friday Reports we noted the proportions of sequenced samples of the newer Omicron sub-lineages. CoVariants provides easily accessible visualisations of sequence frequencies. It is important to be aware that sequenced samples may not be representative of total cases, and that the data is dependent on countries submitting samples to GISAID.

In the United States and Portugal, the Omicron subvariants shown in blue are now more common than the older Omicron ancestors shown in purple. In the US clade 22C (BA.2.12.1) is most common. In Portugal clade 22B (BA.5) is the most commonly reported variant. In the UK, around half of samples are from the newer Omicron sub-variants, primarily BA.5 but with some BA.2.12.1. In Australia, BA.2 is still dominant.

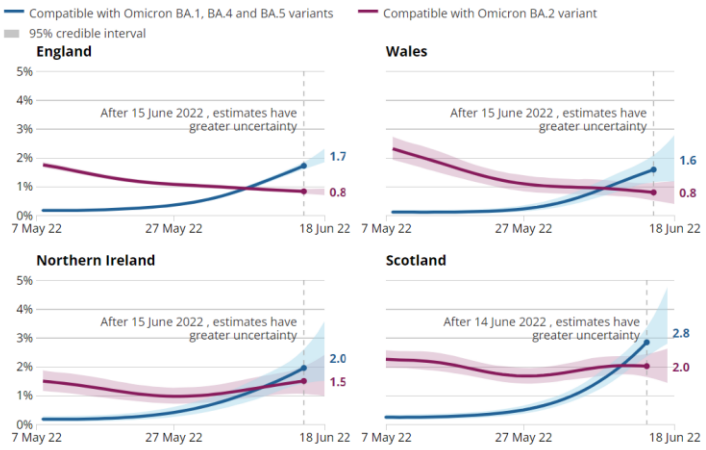


The latest infection survey report for the UK (link) shows the proportion of people testing positive for COVID-19 variants with S-gene target failure ('SGTF'). BA.2 does not have SGTF, while BA.4 and BA.5 do. The data suggest that the prevalence of the new sub-variants has increased over time and BA.4 and BA.5 now represent around two thirds of total infections. (Note that this is a weekly random community survey and therefore not affected by rates of testing in the community.)

It can be seen though that the BA.2 variants are not falling away in the same way that we previously saw when a variant is usurped. This is likely to be the effect of BA.2.12.1, which as previously noted is more common in the USA and also does not exhibit SGTF.

Figure 6: In the most recent week, the percentage of people testing positive for COVID-19 infections compatible with Omicron variants BA.1, BA.4 and BA.5 increased across the UK

Modelled daily percentage of the population testing positive for COVID-19 on nose and throat swabs compatible with Omicron BA.1, BA.4 and BA.5 variants and the Omicron BA.2 variant, UK, 7 May to 18 June 2022



Source: Office for National Statistics – Coronavirus (COVID-19) Infection Survey

Variant-specific symptoms of COVID-19 (link)

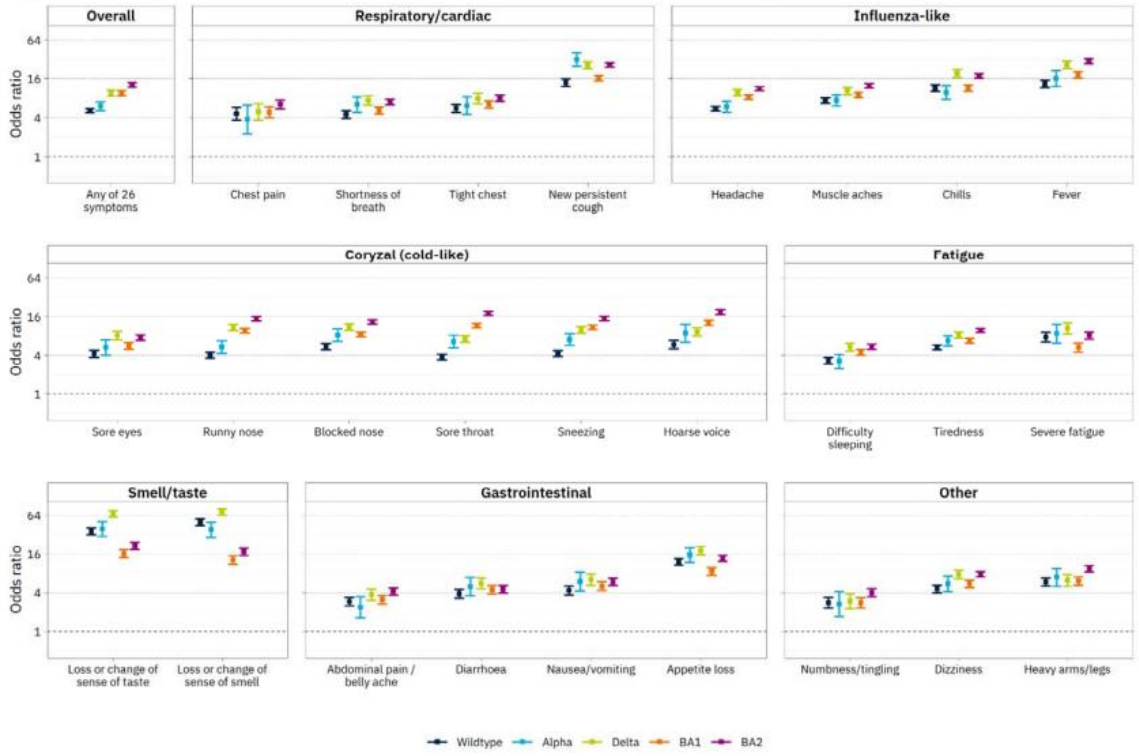
A pre-print paper has used data from the REACT-1 community infection prevalence study to compare symptoms associated with infection with different SARS-CoV-2 variants. Participants were selected randomly from NHS patient registers and were asked to provide self-administered throat and nasal swab samples for PCR testing. Participants also completed questionnaires which included questions on demographic variables, behaviour, and a list of 26 potential recent symptoms.

Data from June 2020 and March 2022 was used, partitioned into different phases depending on which variant was dominant at the time. Between January and March 2022, sequencing data was used to identify participants infected with BA.1 and BA.2. In total, over 1.5m participants, of whom 17,448 were swab positive, were included in the study.

Logistic regression models were used to estimate the risk of PCR swab-positivity for each variant, conditional on experiencing each of the 26 symptoms.

The authors found that loss or change of sense of smell and taste were less predictive of swab positivity for Omicron than for other variants, and that cold-like symptoms were more predictive for Omicron than for previous variants. When comparing BA.2 with BA.1, they found that those with BA.2 were more likely to be symptomatic and were more likely to report that their symptoms affected their day-to-day activities ‘a lot’.

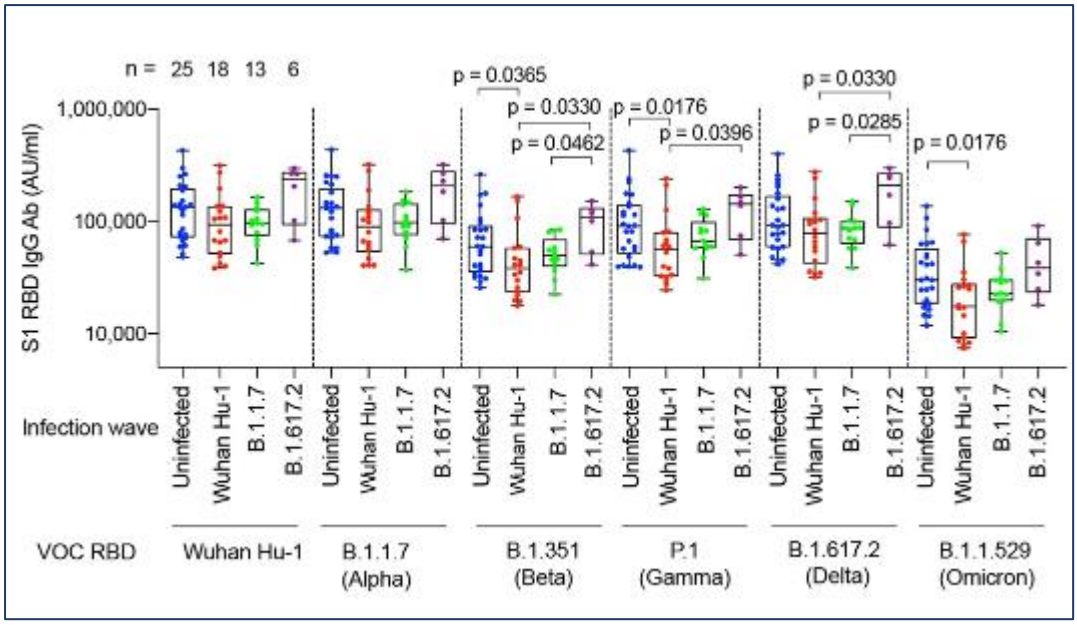
Figure 2 Comparison of ORs for swab positivity based on presence or absence of any of 26 symptoms surveyed across five variant-phases of REACT-1. ORs are derived from logistic regression models with swab positive (1/0) as the outcome variable, adjusted on age, sex and vaccination status. Bars show 95% confidence intervals. ORs are higher in BA.2 than BA.1 for all symptoms. Fever and cough have the highest ORs for BA.1 and BA.2, while loss of smell and taste have the highest ORs in all previous variants.



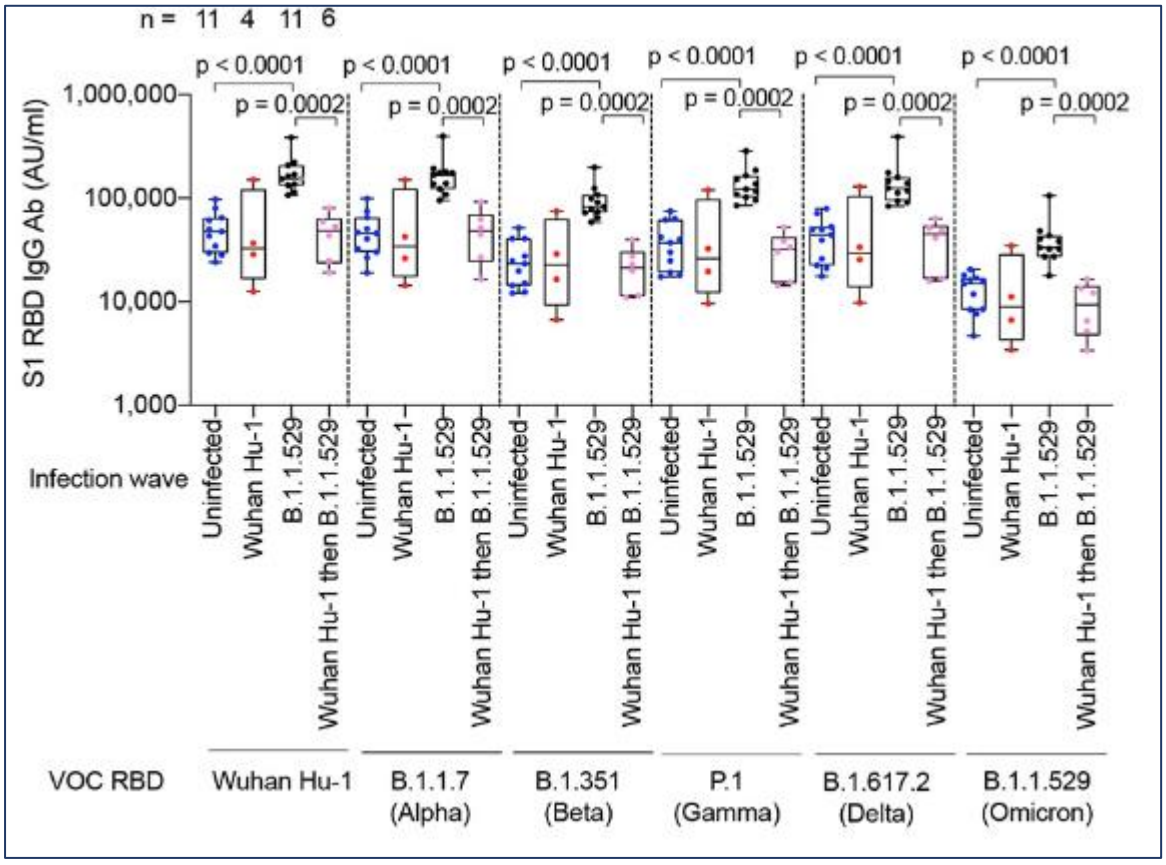
Immune boosting by Omicron depends on previous SARS-CoV-2 exposure (link)

A study by Imperial College London investigated antibody, T cell and B cell immunity against Omicron BA.1 (Pango lineage B1.1.529) and previous variants of concern among 731 triple vaccinated healthcare workers. They identified individuals with different combinations of SARS-CoV-2 infection and vaccination histories to study the impact of immune imprinting.

In all infection history sub-groups, immune responses to Omicron were lower than against previous variants (see far right box of image). Those who were infected during the ancestral Wuhan Hu-1 wave showed a significantly reduced immune response to Beta, Gamma and Omicron compared with infection-naïve participants, as indicated by comparison of the blue (uninfected) and the red (previous ancestral infection) data points in the figure below.



The study also looked at immune responses among healthcare workers who suffered breakthrough infection during the Omicron wave. While those who were infected only with Omicron gained an immunity boost against all variants, as indicated by the black boxes below, prior infection with the ancestral Wuhan strain limited any such boost as indicated by the similar levels of the red and pink boxes. The authors conclude that immune imprinting may impair immune response to future infection.



Clinical outcomes for Omicron vs Delta in California (link)

A preview study reported in the journal Nature shows that Omicron variant infections were associated with substantially reduced risk of progression to severe clinical outcomes relative to Delta variant infections within a large, integrated healthcare system in southern California.

Adjusted hazard ratios (aHRs) for any hospital admission were 0.59 (95% confidence interval: 0.51-0.69) and 0.21 for death. Among cases not previously vaccinated against COVID-19 the aHR was 0.40 (0.33-0.49) for any hospital admission and 0.14 (0.07-0.28) for death. Additionally, infections with the Omicron BA.2 subvariant were not associated with differential risk of severe outcomes compared with BA.1/BA.1.1 subvariant infections.

Medical

Increased neurodevelopmental disorders following exposure to COVID whilst in the womb (link)

A study of over 7,700 babies delivered between March and September 2020 in the USA has revealed that the 222 who were exposed to COVID before birth were more likely to be diagnosed as having a neurodevelopmental disorder during their first year of life.

After adjusting for demographic and clinical factors, for all births the odds ratio for those whose mothers had tested positive was 1.86 (95% CI 1.03 – 3.36), but this increased for those where the positive test was in the third trimester to 2.34 (1.23 – 4.44).

Clearly the confidence intervals around these results are wide, reflecting the relatively low number of births where the mother is known to have had COVID, and the paper notes that follow-up studies are needed to confirm the results.

Effectiveness of Evushield during the US Omicron surge (link)

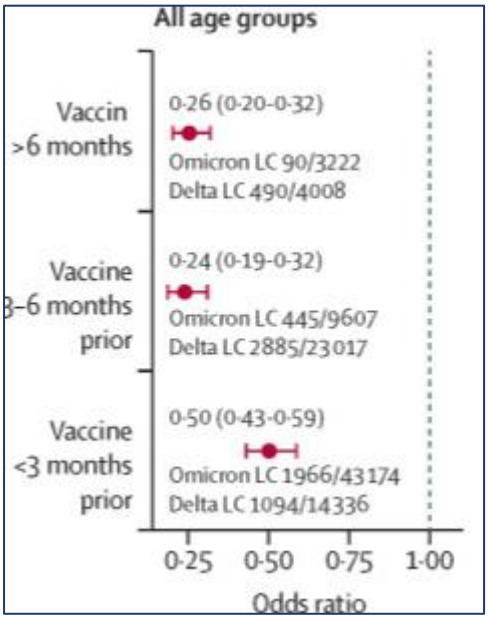
A pre-print study based on data from the national health care databases of the US Department of Veterans Affairs has shown that Evushield is an effective intervention among veterans who were immunocompromised or otherwise at high risk for adverse COVID-19 outcomes. The study took place between January and April 2022 and compared a cohort of 1,848 patients treated with at least one dose of intramuscular tixagevimab/cilgavimab with matched controls selected from 251,756 patients.

Patients treated with Evushield had a lower incidence of SARS-CoV-2 infection (HR 0.34; 95%CI 0.13-0.87), COVID-19 hospitalisation (HR 0.13; 95%CI 0.02-0.99), and all-cause mortality (HR 0.36; 95%CI 0.18-0.73) compared to matched controls.

Long Covid

Risk of Long COVID associated with Delta versus Omicron variants (link)

A UK study used the ZOE app to to study the risk of Long COVID (LC) associated with Omicron compared with the risk from Delta infections. LC was defined as new or ongoing self-reported symptoms 4 weeks or more after the start of acute Covid-19. Omicron infections were deemed to be those occurring in the period 20 December 2021 to 9 March 2022, while people testing positive in the period 1 June to 27 November 2021 were deemed to have Delta infection. Participants were those testing positive in the relevant periods. All participants were vaccinated, with no record of prior SARS-CoV-2 infection.



Among Omicron period cases, 2,501 (4.5%) of 56,003 people experienced LC and, among Delta period cases, 4,469 (10.8%) of 41,361 people experienced LC. After adjusting for vaccination timing to allow for effects of waning immunity, Omicron cases were less likely to experience LC, with an odds ratio ranging from 0.24 (0.20–0.32) to 0.50 (0.43–0.59).

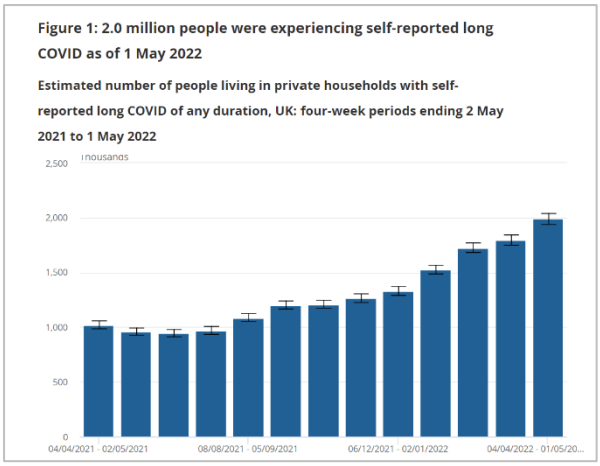
While the relative risk of LC is lower with Omicron, the very high numbers of infections associated with this variant mean that absolute numbers of LC cases will be high.

Long COVID numbers increase in the UK (ONS) (link)

The monthly study on those with Long COVID (LC) symptoms in the UK continues to show rising cases. Whilst the study has come under criticism for relying on self reporting of LC symptoms, the trend appears clear.

With a threshold of 4 weeks of symptoms post an infection to be included in the figures, with the significant BA.1 and BA.2 waves now beyond that time period it is maybe not surprising that there has continued to be an increase.

Of the 2.0m people now estimated to have LC symptoms, over 70% (1.4m) say that the symptoms adversely affect their ability to undergo day-to day-activities, with 20% saying that they have been “limited a lot”.



In terms of length of symptoms, over 800,000 are estimated to have had them for over a year, with over 350,000 now having experienced symptoms for over two years (and thus having been infected in the initial wave in March and April 2020).

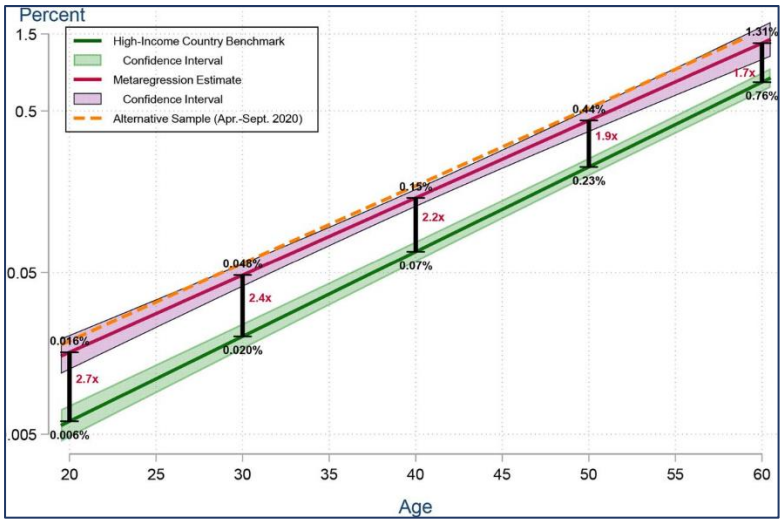
Data

Infection Fatality Rate (IFR) analysis shows higher levels in less developed countries (link)

Many less developed countries appeared to have lower infection fatality rates (IFRs) and COVID deaths than more developed ones, whereas intuitively less sophisticated healthcare systems, greater poverty etc might have suggested the opposite.

However, issues around testing and the fact that many of these countries have much younger population profiles (and thus have lower IFRs, all other things being equal) have led many to be sceptical of any published data.

A study published in the BMJ has analysed excess mortality by country and concludes that in reality IFRs are indeed much higher in less developed countries in the pre-vaccination period and were up to 3 times higher. Of interest, the relative difference appears to be higher at younger ages.



With the initial vaccination of populations having been rolled out much faster in richer countries, this contrast will only have increased during subsequent waves of the virus. Similarly, ongoing booster programmes will prolong the divide between the richer and poorer countries as the latest variants circulate the world.

Outcomes of SARS-CoV-2 reinfection (link)

A pre-print study used the national health care databases of the US Department of Veterans Affairs to show that, compared with people with first infection only, those who are reinfected have increased risks of all-cause mortality, hospitalisation and other adverse health outcomes.

The study included 257,427 people with first infection only, 38,926 with two or more infections and 5,396,855 people with no record of infection. The average age was 61 in the infected group.

The study compared incidence of outcomes in the 180 days following reinfection with incidence of outcomes in the group that had only one infection. The observation period started for the single infection group on an assigned "reinfection" date, based on the typical lag between first and second reinfections in the reinfected group.

All-cause mortality was around double and risk of hospitalisation was trebled in the reinfected group compared with the single infection group.

Outcome	HR (95% CI)
All-cause mortality	2.14 (1.97, 2.33)
Hospitalization	2.98 (2.83, 3.12)
At least one sequela	1.82 (1.78, 1.88)
Cardiovascular	2.36 (2.23, 2.51)
Coagulation and hematologic	2.22 (2.05, 2.41)
Diabetes	1.62 (1.49, 1.76)
Fatigue	2.4 (2.22, 2.58)
Gastrointestinal	1.69 (1.58, 1.8)
Kidney	1.7 (1.52, 1.9)
Mental health	1.97 (1.9, 2.04)
Musculoskeletal	1.29 (1.2, 1.38)
Neurologic	1.39 (1.32, 1.46)
Pulmonary	2.49 (2.34, 2.65)

The study also found that, compared with non-infected controls, the risk of adverse outcomes increased in a graded fashion according to the number of infections. Other commentators have suggested that suffering multiple reinfections may itself be an indicator of compromised health.

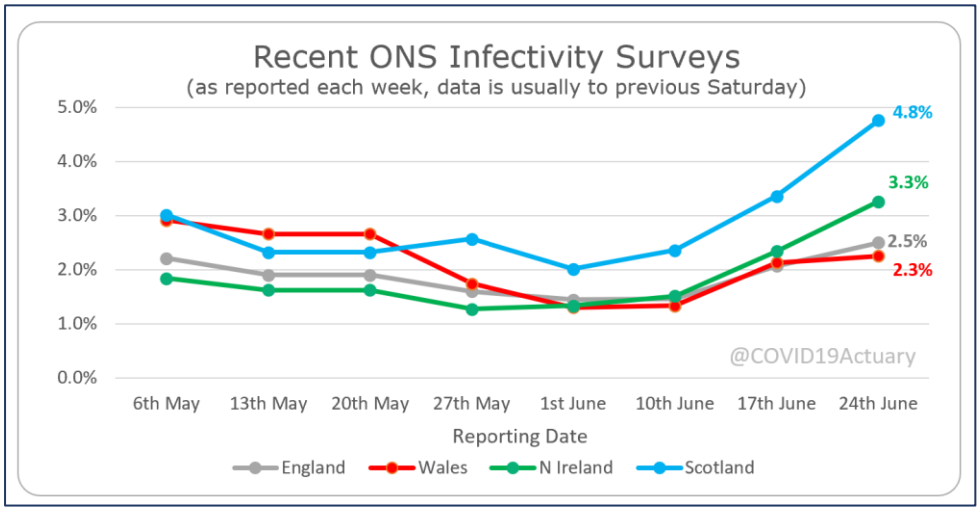
The authors conclude that reinfection adds non-trivial risks of all-cause mortality, hospitalisation and adverse health outcomes. Therefore reducing the overall burden of COVID-19 death and disease will require strategies for reinfection prevention.

It should be noted, however, that this pre-print has attracted a great deal of comment and scrutiny on social media, both because of the importance of the topic and concerns about aspects of the data and methodology. We expect that formal peer-review will likely result in some modifications to the paper.

ONS Infection Study (link)

Returning to the ONS infection prevalence study referred to earlier, it confirms that we are now in a further wave, following a bottoming out of infection levels around a month ago. Over the last two weeks the increases have ranged from around 70% in England and Wales with a doubling in Northern Ireland and Scotland.

It should be noted that the most recent week's increases have been lower in England and Wales, giving some optimism that we will see a peak well short of those seen earlier in the year (eg 7.5% in respect of BA.2 in England).

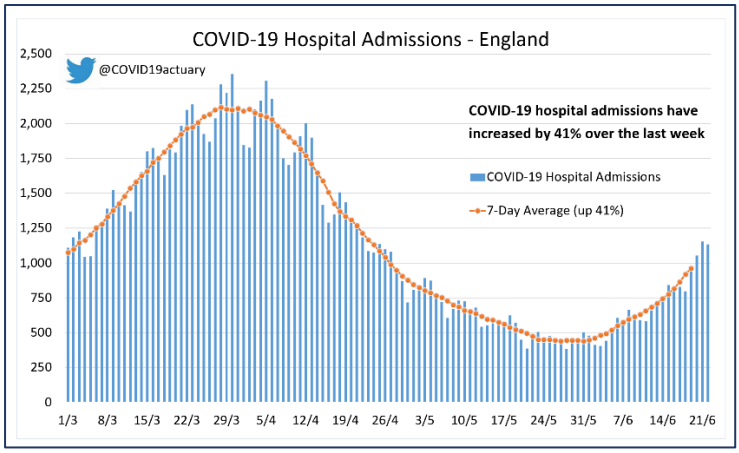


Hospital Admissions Increase Too

Along with the rise in prevalence, June has also seen a significant increase in admissions, with a doubling since the beginning of the month. Currently the daily average is running at around 960, and is likely to rise well above 1,000 with the current growth of 41% suggesting a doubling every 14 days.

As can be seen from the chart below, one further doubling would take us back broadly to the level of admissions seen during the BA.2 wave (and indeed the BA.1 wave before that).

It should be noted that not all admissions with a positive COVID diagnosis are primarily being treated for it. The proportion of COVID beds occupied where it is the primary diagnosis was typically around 75% prior to Omicron, but is now at a much lower level of just under 40%.



And Finally…

Using dogs to detect COVID is not to be sniffed at (link)

A dogged search for an offbeat story to finish with led us to this scientific paper published on the American website PLOS One. A team of French researchers has concluded that sniffer dogs can be very accurate in detecting COVID based on samples collected from the armpit or nasal passage, as the results below show.

Amongst the points noted by the researchers are that *"the dog handlers, (and the dogs…) were blinded with regards to the COVID status"*, and that the dogs were given toy rewards.

The practicality of using dogs to directly assess COVID status is discussed, though it notes that some people's fear of dogs may make this difficult (presumably direct sniffing of people's armpits is not envisaged), and that the time for training and certification of an adequate supply of animals would be an issue too. Nevertheless further studies are being undertaken to see whether there are suitable applications by the French High council for Public Health.

	Total, n	Positive sample, n	Sensitivity (95% CI*)	Specificity (95% CI*)
Dog 1 (Oxmo)	89	29	90% (73 to 98)	95% (86 to 99)
Dog 2 (Jinko)	203	73	100% (95 to 99)	86% (79 to 92)
Dog 3 (Leyko)	144	42	95% (84 to 99)	91% (84 to 96)
Dog 5 (Joye)	226	70	100% (95 to 100)	90% (85 to 95)
Dog E (Ortie)	23	7	71% (29 to 96)	100% (79 to 100)

24 June 2022